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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/080,979	02/22/2002	Phillip Dan Cook	ISIS-5028	9967
34138	7590	08/09/2005	EXAMINER	
COZEN O'CONNOR, P.C. 1900 MARKET STREET PHILADELPHIA, PA 19103-3508			BOWMAN, AMY HUDSON	
			ART UNIT	PAPER NUMBER
			1635	

DATE MAILED: 08/09/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	Application No. 10/080,979	Applicant(s) COOK ET AL.	
	Examiner Amy H. Bowman	Art Unit 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
  - If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
  - If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
  - Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 11 July 2005.
- 2a) ☒ This action is **FINAL**.                      2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1,3-7,9-12 and 14-16 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1,3-7,9-12 and 14-16 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)                        | 4) <input type="checkbox"/> Interview Summary (PTO-413)                     |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)               | Paper No(s)/Mail Date. _____  |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date <u>6/8/2005</u>  | 6) <input type="checkbox"/> Other: _____                                    |

## **DETAILED ACTION**

### ***Status of Application/Amendment/Claims***

Applicant's response filed 7/11/2005 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 2/11/2005 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

With entry of the amendment filed on 7/11/2005, claims 1, 3-7, 9-12 and 14-16 are pending in the application. Applicant has canceled claims 2, 8, 13, and 17-22.

### ***Response to Arguments--Double Patenting Rejection***

Claims 1-11 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 2 of U.S. Patent No. 6,753,423 for the reasons of record set forth in the office action mailed 2/11/2005.

Applicant argues that the amendment to instant claim 1 regarding the rate of clearance of the oligonucleotide is not obvious in view of claim 2 of patent '423. Applicant argues that the rate of clearance of the oligonucleotide containing two modifications is not obvious in view of claim 2 of patent '423.

On the contrary, the oligonucleotide of the method of claim 2 of patent '423 is considered to necessarily be cleared from the circulation at approximately the same rate

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as a second oligonucleotide wherein said second oligonucleotide has no sterol moieties covalently bonded thereto, as instantly claimed. Claim 2 of patent '423 teaches each of the method steps of the instant claims, so the method of '423 is considered to have the same outcome.

Claims 1-11 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 3 of copending U.S. Patent Application No. 10/780,439 for the reasons of record set forth in the office action mailed 2/11/2005. Applicant has requested abeyance until allowable matter is identified in one of the cases.

### ***New Objections/Rejections***

#### ***Claim Objections***

Claim 7 is objected to because of the following informalities: The word "endothelial" is spelled "endothetial". Appropriate correction is required.

### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3-7 and 9-11 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject

matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claims 1, 3-7 and 9-11 are directed to methods of modulating the expression of a nucleic acid in the hepatic system of a mammal, comprising administering an antisense oligonucleotide having at least two sterol moieties, more cholesteryl moieties, covalently bonded thereto, more specifically bonded at the 2'-O, 3'-O, or 5'-O positions, and wherein the oligonucleotide is cleared from the circulation at approximately the same rate as a second oligonucleotide having no sterol moieties covalently bonded thereto. Applicant has pointed to page 122, lines 6-9 for support for the amendments to claims 1 and 6. On the contrary, support has not been located on page 122, lines 6-9, for the amendments to the claims regarding the rate of clearance of the oligonucleotide. Neither literal nor implied support for the oligonucleotide being cleared from the circulation at approximately the same rate as a second oligonucleotide without sterol moieties is evident in the instantly filed specification or claims. Further, support is not evident for the concept of the genus of molecules in the instant claims wherein the molecules are cleared from the circulation at approximately the same rate as a second oligonucleotide that is not bonded to sterols. On the contrary, the instant specification discloses that the retention of the oligonucleotide depends on the presence of cholesterol (see page 122, lines 13 and 14).

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 3-7, 9-12, and 14-16 are rejected under 35 U.S.C. 102(a) or (e) as being anticipated by Dean et al. (US 6,312,900 B1).

The invention of the above claims is drawn to methods of modulating the expression of a nucleic acid in the hepatic system of a mammal, methods of preferentially targeting an antisense oligonucleotide to liver cells in a mammal, and methods of treating a mammal, each comprising administering an antisense oligonucleotide having at least two sterol moieties, more specifically cholesteryl moieties, covalently bonded thereto, more specifically bonded at the 2'-O, 3'-O, or 5'-O positions. The invention is further drawn to clearance of the antisense oligonucleotide from the circulation at approximately the same rate as a second oligonucleotide having no sterol moieties covalently bonded thereto. The liver cells are specified to be endothelial cells.

Dean et al. teach a method of inhibiting expression of a nucleic acid comprising contacting cells or tissues with an antisense oligonucleotide, wherein the

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oligonucleotide comprises at least one lipophilic moiety, more specifically cholesteryl moieties, which enhances the cellular uptake of said antisense oligonucleotide (see claims 1, 2 and 27). Dean et al. teach that the oligonucleotides of the invention are contacted with animal cells either *in vivo* or *ex vivo* (see column 11) and specifically teach targeting nucleic acids in adult mice *in vivo* and resultant treatment of tumor growth (see example 4). Dean et al. teach that the lipophilic moieties may be linked to the oligonucleotide at several different positions on the oligonucleotide, including the 3', 5' or 2' positions (see column 9). Additionally, Dean et al. teach that the oligonucleotides can be delivered to the liver (see column 15). Dean et al. teach delivery via colloidal dispersion systems, wherein liposomes naturally distribute to cells of the reticuloendothelial system (see column 16). Although Dean et al. are silent as to the rate of clearance of the oligonucleotide compared to an oligonucleotide without cholesteryl moieties, Dean et al. teach each of the instantly claimed method steps. Therefore, the method of Dean et al. would necessarily result in the clearance instantly claimed.

Therefore, the instant invention is anticipated by Dean et al.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amy H. Bowman whose telephone number is 571-272-0755.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within



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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Amy H. Bowman  
Examiner  
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A handwritten signature in black ink, appearing to read 'Andrew Wang', is written over the printed name.

**ANDREW WANG**  
**SUPERVISORY PATENT EXAMINER**  
**TECHNOLOGY CENTER 1600**